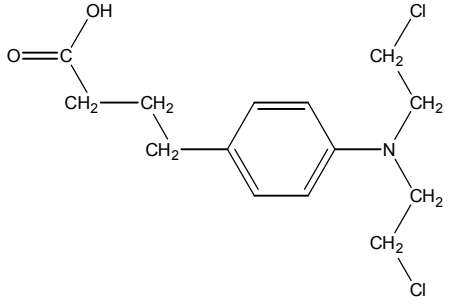
CHLORAMBUCIL
CAS No. 305-03-3
First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

Chloroambucil is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC S.4, 1982; IARC S.7, 1987). Excesses of leukemia were reported in a number of epidemiological studies in which chlorambucil, either alone or in combination with other therapies, was used in treating nonmalignant and malignant diseases. Other cancers have also been associated when chlorambucil, in combination with other agents, was used for treatment. An excess of leukemia in association with chlorambucil was seen in a further study in which 431 previously untreated patients with polycythemia vera were given phlebotomy alone or chlorambucil with phlebotomy and followed for a mean of 6.5 years. Of the 26 cases of acute leukemia that occurred, 16 were in the group receiving chlorambucil. The risk increased with increasing dose and time of treatment (IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of chloroambucil in experimental animals (IARC S.4, 1982; IARC S.7, 1987).When administered by intraperitoneal injection, chlorambucil increased incidences of lymphosarcomas and lung adenomas and adenocarcinomas in mice of both sexes; ovarian neoplasms in female mice; and lymphosarcomas, myelogenous leukemia and reticulum cell sarcomas in male rats (Weisburger et al., 1975; IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987). When the compound was administered topically as the initiator in a two-stage study with croton oil, skin papillomas were induced in mice (IARC V.9, 1975; IARC V.26, 1981; IARC S.4, 1982).

PROPERTIES

Chlorambucil is a white crystalline powder with a slight odor. It is very slightly soluble in water and soluble in ethanol, chloroform, acetone, diethyl ether, and dilute solutions of alkali hydroxides. Chlorambucil is available in the United States as a grade containing 98%-101% active ingredient on a dried basis. When heated to decomposition, it emits toxic fumes of hydrochloric acid and other chlorinated compounds as well as nitrogen oxides (NO_x).

USE

Chlorambucil is used for palliative treatment of chronic lymphocytic leukemia, malignant lymphomas (e.g., lymphosarcoma), giant follicular lymphoma and Hodgkin's disease. The treatment, though not curative, does produce some marked remissions. Other uses for which chlorambucil has been tested include treatment of systemic lupus erythematosis, chronic glomerular nephritis, nephrotic syndrome, psoriasis, cold hemagglutinic disease, Wegener's granulomatosis, chronic hepatitis, and rheumatoid arthritis. Chlorambucil has also been investigated for use in chemosterilization of insects (IARC V.26, 1981). EPA reports, however, that chlorambucil has not been registered as a pesticide.

PRODUCTION

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB, 1997). No domestic suppliers were listed in any *Chemcyclopedia 98* and the *1998 Chemical Buyers Directory* (Rodnan, 1997; Tilton, 1997); however, *Chemcyclopedia* did name a chlorambucil supplier located in Ontario (Rodnan, 1997). In 1983, 37 lb of chlorambucil were imported into the United States (USITCa, 1984). Imports through the principal U.S. customs districts amounted to about 106 lb in 1978 (IARC V.26, 1981). FDA reported that 6.4 million prescriptions were dispensed by retail pharmacies in 1980.

EXPOSURE

The primary routes of potential human exposure to chlorambucil are ingestion, inhalation, and dermal contact. Continuous and intermittent oral treatment schedules are employed for patients treated with chlorambucil. In the former, the daily dose is 0.1 to 0.2 mg/kg body weight and is adjusted according to the response of the disease and bone marrow. In the latter case, it is common to give intermittent 2-week courses of 10 to 20 mg daily with rest periods of 2 to 4 weeks (IARC V.26, 1981). Exposure in the United States is limited not only to patients receiving the drug but also to workers formulating the tablets (HSDB, 1997). NIOSH reported no indication of potential worker exposure in the National Occupational Hazard Survey conducted from 1972 to 1974 (NIOSH, 1976). The National Occupational Exposure Survey, conducted by NIOSH from 1981 to 1983, however, estimated that 3,718 workers, including 2,018 women, were potentially exposed to chlorambucil (HSDB, 1997). Potential occupational exposure may occur during the formulation, packaging, and administration of the pharmaceutical.

REGULATIONS

EPA regulates chlorambucil under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). EPA established a reportable quantity (RQ) under CERCLA of 1 lb and proposed an adjustment of the RQ to 10 lb. The final rule establishes the RQ as 10 lb. EPA's Carcinogen Assessment Group includes chlorambucil on its list of potential carcinogens and regulates it as a hazardous waste under RCRA. In fulfilling the purposes of the Toxic Substances Control Act (TSCA), EPA requires the submission of lists and copies of health and safety studies on chlorambucil or mixtures containing chlorambucil under section 4(a) of TSCA. Chlorambucil is regulated by the FDA under the Food, Drug, and Cosmetic Act (FD&CA). FDA approved chlorambucil under the FD&CA for use as a prescription drug in 1969, noting restrictive

approved clinical use for the treatment of chronic lymphocytic leukemia, malignant lymphomas, and Hodgkin's disease. Drug labeling requirements under the FD&CA also apply to chlorambucil. OSHA regulates chlorambucil as a chemical hazard in laboratories and under the Hazard Communication Standard. Regulations are summarized in Volume II, Table A-14.